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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,185	11/19/2003	Shripad S. Bhagwat	10624-143-999	9314

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EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,185	BHAGWAT ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-25* is/are pending in the application.

4a) Of the above claim(s) *4,6 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5, 7-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 1/29/2008 is acknowledged. The objection to the specification is withdrawn as Applicants have amended the specification to indicate that the parent applications are now patents.

Applicant's arguments over the 35 USC 112, first paragraph rejection have been fully considered and are not found persuasive. In particular, Applicants argue that human testing does not need to occur within the confines of Patent and Trademark Office proceedings. Applicants supply 2 articles (Force et al. and Manning et al.) to show that there is a correlation between *in vitro* kinase activity and *in vivo* treatment of cancer and assert that there is an established correlation between *in vitro* kinase inhibition assays and *in vivo* use. Applicants further assert that it is well-settled that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled and that the clinical success of all claimed compounds is not a statutory requirement for patentability.

In response to the above arguments, it is respectfully pointed out that the articles written by Force et al. and Manning et al. discuss the identification of drug targets for therapeutic intervention. In both articles it is discussed that screening for chemical libraries is performed to identify possible inhibitors in which candidates go through a process called high-throughput screening. Compounds go through in vitro studies to determine selectivity and efficacy of the compounds. However, it is known that every compound that is tested in the in vitro assay and shown to have high efficacy and selectivity may "display markedly different and even unexpectedly nonspecific activity in

vivo" (Force et al., page 1200, last paragraph). Further, Force et al. goes on to discuss the testing of the compounds in different disease states (see page 1201 under the section To the Bedside) and gives a table of agents that have strong preclinical data to suggest that they may be efficacious in treating different diseases. Further, disease states are discussed in which agents are in clinical trials or still going through preclinical drug development. Manning et al. implicate a role of JNK in cancer but does not express that every modulator of JNK activity will effectively treat all cancers. Accordingly, it is well expected that compounds not only go through extensive in vitro testing, but also go through extensive testing in in vivo assays to verify that the compound is capable of treating a particular disease.

Further, it is requested that Applicant refer to section 2164 of the MPEP in which the enablement requirement is explained in detail. It is noted that the MPEP states that "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied". Following this statement is a discussion explaining that if one skilled in the art would be able to determine an appropriate dosage or method of use without undue experimentation, based on knowledge of the compounds having similar physiological or biological activity, then this would be sufficient to satisfy the enablement requirement. See MPEP § 2164.01. Because the arguments are not found persuasive, the rejection is being maintained and is given below for Applicants convenience.

Applicants have amended claim 1 in an attempt to overcome the 35 USC 112, first paragraph (scope of enablement) rejection. The rejection was made based on the fact that the specification does not reasonably provide enablement for the prevention of all diseases (cancers) with the indazole compounds. Applicants have amended the claim to remove the "prevention" terminology; however, the claim still broadly claims treatment of cancer, which includes all cancers. As expressed in the rejection, there is no data exemplifying treatment of all types of cancer with the compounds of the invention. Accordingly, a modified form of the rejection is being given below.

Applicant's filing of terminal disclaimer is sufficient to overcome the Double Patenting rejection over US Patent 7,220,771. Applicants assert that they will consider filing a terminal disclaimer in connection with co-pending applications 11/512,836 and 11/376,786. Because a terminal disclaimer has not yet been filed, the Double Patenting rejections over the co-pending applications are being maintained.

Claim Rejections – 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, and 7-17 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

1) The nature of the invention and breadth of the claims: The nature of the invention and breadth of the claims is drawn to a method for treating cancer comprising administering an effective amount of a compound having the structure in claim 1 (in particular the elected species 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole).

2) The presence or absence of working examples and the amount of direction or guidance presented: In the instant case, working examples are presented for measuring the activity of the compounds of the invention in various assays, such as JNK2 assay, JNK3 assay, Jurkat T-cell 11-2 Production Assay, rat in vivo LPS-induced TNF-α Production assay and various other assays (see Examples 435-509). These assays verified the ability of the compounds to inhibit the various

receptors and their corresponding IC50 value. However, there is no data exemplifying treatment of any type of cancer with the compounds of the invention.

The extent of the studies of the present invention is to determine the activity of the various indazole compounds of the invention in inhibiting tyrosine kinase signal transduction. This determination is done via various protein kinase assays. The determination of a particular claimed compound in the treatment of cancer requires the synthesis of the compound, formulation into a suitable dosage form, and testing in a known assay that is correlated with clinical efficacy. Applicants state on pages 40-42 that the compounds of the invention are useful in treating cancer and list various cancers that can be treated. However, there are no further examples exemplifying the effectiveness of the compounds in an animal model of any particular cancer with no effective dose range being determined in the treatment of cancer.

The issue in *Ex parte Balzarini* 21 USPQ2d 1892 concerned HIV treatment and the Board of Patent Appeals and Interferences wrote "while the *in vitro* testing performed on these anti-viral compound appears to be useful as a screening tool in order to determine which of these anti-viral compounds are candidates for further testing to determine if they possess *in vivo* utility, the *in vitro* tests were not predictive of *in vivo* efficacy". Furthermore, the issue in *Fujikawa v. Wattanasin* 39 USPQ2d 1895 was adequacy of *in vitro* testing of inhibitors of cholesterol biosynthesis and U.S. Court of Appeals Federal Circuit wrote, "*in vitro* results, in combination with a known correlation between such *in vitro* results and *in vivo* activity, may be sufficient to

establish practical utility". A working example in *in vivo* experiments showing that the compounds would effectively treat the claimed diseases is lacking.

3) The state of the prior art: The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual" or not provided in the specification, *Ex parte Jovanovics*, 211 USPQ 907, *In re Langer*, 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

It is art recognized that a perturbation of protein tyrosine kinase (PTK) activity results in a variety of diseases, including cancer (see Al-Obeidi et al., Oncogene (2000) 19, 5690-5701). In the Introduction of this paper, it is stated that many PTK's have been implicated in human cancer and give examples of some specific PTK's that are implicated in different types of cancer. Al-Obeidi et al. goes on to discuss the

approaches to the development of inhibitors and discusses compounds that have been tested in pre-clinical and clinical studies. Al-Obeidi et al. discusses that inhibitors of some PTK's may be useful for the treatment of a number of diseases and that a large number of PTK inhibitors have been developed and that several are undergoing clinical trials. Al-Obeidi et al. conclude that it is likely that several clinically useful PTK inhibitors will be on the market within the next decade, making it evident that not all of the PTK inhibitors that will be synthesized will necessarily be effective in clinical situations and should be tested.

4) The quantity of experimentation necessary: "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed Cir. 1993)". Undue experimentation would be required in order to practice Applicant's invention because there are no examples provided in the specification in an approved animal model for any type of cancer with any indazole compound and in particular the elected compound 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole. One would have to determine a useful model that correlates with clinical efficacy, a dosage range would need to be determined as well as a route of administration. Further, if any of the above failed, then the artisan would have to start over again in an effort to determine the suitable methods, dosage ranges and routes of administration in which to determine if the compounds will work to treat cancer.

Claims 1, 3, 5 and 7-17 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the activity of various indazole compounds that inhibit, modulate or regulate tyrosine kinase signal transduction, does not reasonably provide enablement for the treatment of all cancers with the indazole compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1) The nature of the invention and breadth of the claims: The nature of the invention and breadth of the claims is drawn to a method for treating cancer comprising administering an effective amount of a compound having the structure in claim 1 (in particular 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole).

2) The presence or absence of working examples and the amount of direction or guidance presented: In the instant case, working examples are presented for measuring the activity of the compounds of the invention in various assays, such as JNK2 assay, JNK3 assay, Jurkat T-cell 11-2 Production Assay, rat in vivo LPS-induced TNF-α Production assay and various other assays (see Examples 435-509). These assays verified the ability of the compounds to inhibit the various receptors and their corresponding IC50 value. However, there is no data exemplifying treating all types of cancer with the compounds of the invention. There is no data presented in accepted animal models of various types of cancer suggesting that indazole compounds would show clinical efficacy in treating all cancers.

3) The state of the prior art: The state of the art for the treatment of various types of cancer is high.

4) The quantity of experimentation necessary: "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed Cir. 1993)". Undue experimentation would be required in order to practice Applicant's invention because there are no examples provided in the specification showing that all cancers would be treated following administration of indazole compounds. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting

license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3 and 14-17 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 9-10 of copending Application No. 11/512,836. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to a method for treating disease (cancer) comprising administration of an indazole compound (3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole).

The claims of application 11/512,836 are drawn to a method for treating chronic lymphocytic leukemia comprising administration of 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole. The applications are obvious over the other in that they both involved treatment of a cancer with indazole compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3 and 14-17 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/376,786. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to a method for treating disease (cancer) comprising administration of an indazole compound (3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole). The claims of application 11/376,786 are drawn to a method for treating acute myelogenous leukemia comprising administration of 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole. The applications are obvious over the other in that they both involved treatment of a cancer with indazole compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617